IN THE CIRCUIT COURT, FOURTH JUDICIAL CIRCUIT, IN AND FOR DUVAL COUNTY, FLORIDA

CASE NO.: 00-02790-CA
DIVISION: CV-B

MICHAEL L. McMULLIN and
KELLI McMULLIN,
Plaintiffs,

vs.

U.S. SMOKELESS TOBACCO COMPANY,

Defendant

****

ORAL DEPOSITION OF

KENNETH RAMOS, Ph.D.

OCTOBER 7, 2002

****

Deposition of KENNETH RAMOS, Ph.D. taken on the 7th day of October, 2002, beginning at 1:55 p.m., in the offices of Skadden, Arps, Slate, Meagher & Flom, LLP, 1600 Smith Street, Suite 4400, Houston, Texas 77002, before Elaine P. Maspero, RPR, Certified Shorthand Reporter and Notary Public in Harris County, for the State of Texas, pursuant to the Florida Rules of Civil Procedure.

ORIGINAL

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the Industry Documents Library: http://www.industrydocuments.ucsf.edu/docs/lgql0001

APPEARANCES

FOR THE PLAINTIFFS:

Mr. Robert F. Spohrer
Florida Bar No. 0184500
Spohrer Wilner Maxwell & Matthews, PA
701 West Adams Street, Suite 2
Jacksonville, Florida 32204
904/354-8310

FOR THE DEFENDANT:

Mr. Chester J. Wrobleski
-and-
Mr. Jonathan R. Kuhlman
Jacob, Medinger & Finnegan
1270 Avenue of the Americas
New York, NY 10020
212/332-7700

http://legacy.library.ucsf.edu/tid/vpq07a00/pdf
Source: https://www.industrydocuments.ucsf.edu/docs/lqgl0001

I N D E X

NO.	DESCRIPTION	PAGE
	EXAMINATION BY MR. SPOHRER	4
1	Studies Involving Oral Exposure of Laboratory Animals to Smokeless Tobacco	23
2	Handwritten note	23
3	List of billing activity	53
	SIGNATURE PAGE	68

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

KENNETH RAMOS, Ph.D.,

having been first duly sworn, testified as follows:

EXAMINATION

BY MR. SPOHRER:

Q. Doctor, could I have your full name, please?

A. Kenneth Ramos.

Q. And where is your office located, please?

01:55 A. In the Department of Pharmacology and Department of Veterinary Medicine at Texas A&M University.

Q. You are a full time employee there?

A. That's correct.

01:56 Q. What is your specialty or expertise in, please, sir?

A. Toxicology and molecular biology.

Q. Okay. When were you first contacted by anyone with respect to this lawsuit?

01:56 A. Early part of July of this year.

Q. And who contacted you?

A. Mr. Wrobleski.

Q. Did you know him before that contact?

A. I did.

01:56 Q. How did you know him?

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

01:56 A. I had interacted with him in the past on other cases.

Q. How many other cases?

A. Two, I believe.

01:56 Q. And what did they involve, please?

A. Health effects of smokeless tobacco.

Q. Both cases?

A. I believe so.

Q. Okay. And did you give a deposition in

01:57 either of those cases?

A. No.

Q. What did the first of those two cases involve, what type of claim was made by the plaintiff?

01:57 A. One case was a case related to bladder cancer.

Q. Um-hmm.

A. And I cannot recall the second case.

Q. Are either of those cases still pending to your knowledge?

A. Not to my knowledge.

Q. And you did not testify in either of those cases you said. Right?

A. That's correct. None of them progressed.

01:58 Q. Did the second case involve some type of

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

cancer?

A. I don't remember.

Q. Okay. How long ago were these cases?

A. A while back, years.

Q. 10 years, five years?

A. Not 10 years.

Q. Five years?

A. Between one and five years.

Q. Okay. And did you express an opinion to Mr. Wrobleski in both of those cases?

MR. WROBLESKI: Object to the form.

Q. (BY MR. SPOHRER) Yes?

A. Could you clarify that question?

Q. I don't know if I can. In either of those cases, did you formulate an opinion and express that opinion to Mr. Wrobleski?

A. I don't remember.

Q. Okay. Prior to your contact by Mr. Wrobleski in the first of those cases five years ago, we'll say or thereabouts, had you done any other work for U.S. Tobacco, U.S. Smokeless Tobacco or any related companies?

A. I don't think so.

Q. Okay. We have been given a copy of a CV for you, sir, which lists a number of articles and

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

publications. Do any of them relate to smokeless tobacco?

A. No.

Q. Prior to your contact by Mr. Wrobleski, had you done any research on any aspect of smokeless tobacco?

A. Not directly on smokeless tobacco, but I've done extensive research on chemicals that are present in smokeless tobacco.

Q. Okay. Such as which chemicals?

A. Polycyclic aromatic hydrocarbons, for short PAHs.

Q. And in what context did you do that research?

A. Laboratory, experimental research.

Q. For a specific client or --

A. No, no. Basically fundamental.

Q. Fundamental research?

A. Federally sponsored research activity.

Q. Okay. Are polycyclic aromatic hydrocarbons found in smokeless tobacco?

A. Yes, sir.

Q. Which ones are found in smokeless tobacco?

A. Benzpyrene for example.

Q. Any others?

http://legacy.library.ucsf.edu/tid/vnb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

A. That's major one that is cited, but...

Q. Is benzopyrene a carcinogen?

A. Benzopyrene is classified as a laboratory animal carcinogen, yes.

Q. Is it a human carcinogen in your opinion?

A. No, it has not been demonstrated to be a human carcinogen.

Q. Any other substances in moist smokeless tobacco which you believe are, first, animal carcinogens?

A. Could you restate the question?

Q. Sure. Do you know of any -- well, first of all, do you know the ingredients, all the ingredients of Copenhagen or Skoal?

A. I know many of the ingredients in Copenhagen and Skoal.

Q. Have you been given a list of all the ingredients?

A. The course of my studies, I have become familiar with many of the chemicals in smokeless tobacco, yes.

Q. I understand that, Doctor, but my question is: Do you have somewhere or have you ever seen a list of all of the constituents or ingredients of Copenhagen or Skoal?

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

A. I have seen that, yeah, in the past.

Q. You have?

A. Yeah.

Q. Where was that?

A. Partial listings, for instance, in the Surgeon General's report.

Q. But with regard to this company's products specifically, do you believe you have ever seen a comprehensive list of all of the ingredients?

A. No, I have not.

Q. Okay. Is polonium 210 a carcinogen?

A. Polonium 210 is regarded as a putative animal carcinogen.

Q. What does that mean?

A. That in -- under certain conditions it may be associated with a carcinogenic response in experimental model systems.

Q. Do you believe that polonium 210 is a human carcinogen?

A. I don't believe that's been demonstrated.

Q. It is nuclear waste, isn't it?

A. It's an alpha emitting radioactive particle.

Q. It is nuclear waste, isn't it?

A. It's an alpha emitting --

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

Q. Fair enough.

A. -- particle.

Q. As such is it considered to be a human carcinogen?

A. I do not know.

Q. Don't know. Okay.

Do you know whether the defendant's products contain polonium 210?

A. I do not know that.

Q. Okay. Do you know whether the defendant's products contain cadmium?

A. Smokeless tobacco has been reported to contain heavy metals.

Q. And do you believe that Copenhagen and Skoal contain heavy metals?

A. I have no basis to --

Q. You don't know?

A. -- to make that statement.

Q. I'm just asking, you have seen a partial list of ingredients.

A. Correct.

Q. That's not been on any list that you have seen?

A. Cadmium is cited in the Surgeon General report.

http://legacy.library.ucsf.edu/tid/vbp07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

Q. Okay. And is cadmium a carcinogen?

A. Do you mean a laboratory animal carcinogen?

Q. Either.

A. I guess one would have to, you know, qualify the --

Q. Let's start with that. In your opinion is cadmium a carcinogen in laboratory animals?

A. There is experimental evidence for some carcinogenic activity in laboratory animals by cadmium, yes.

Q. Do you believe that cadmium is a human carcinogen?

A. I don't think that's been demonstrated.

Q. Okay. Are you familiar with an agent called coumarin?

A. I think so.

Q. Okay. Is coumarin a carcinogen?

A. I do not know.

Q. Do you know whether it is a laboratory carcinogen?

A. What I know about coumarin is not in the context of carcinogenesis so I do not know.

Q. Tell me what you know about that substance, please?

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Document hosted at industrydocuments.ucsf.edu/docs/lqgl0001

02:06 A. I recognize coumarin in the context of anticoagulant activity.

Q. I'm not saying coumadin. I'm saying coumarin.

02:06 A. Oh, coumarin.

Q. Yes, sir.

A. Okay. No, I'm not familiar with it.

Q. Have you ever heard of that substance?

A. I have, yeah.

02:06 Q. Okay. Do you know whether or not it is a carcinogen or not?

A. I do not.

Q. Okay. Doctor, which polycyclic aromatic hydrocarbons are in ST and I think you told me

02:07 benzopyrene and that that is known as a laboratory carcinogen. Correct?

A. Yes, laboratory animal carcinogen.

Q. Laboratory animal carcinogen. Is it in your view not a human carcinogen?

02:07 A. Yes, in my view it has not been demonstrated to be a human carcinogen.

Q. What would it take to satisfy you -- what do you need to make the jump from whether something is a laboratory animal carcinogen to a human

02:07 carcinogen?

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lqgl0001

MR. WROBLESKI: Object to the form.

A. Could you restate the question?

Q. (BY MR. SPOHRER) Sure. In your experience, are some substances first identified as carcinogens in laboratory animals and then later identified as human carcinogens?

Strike that. You are having trouble with that question too.

What is it about benzopyrene that persuades you that that it is not a human carcinogen?

A. To be quite honest, I actually preferred the question the other way around. I think the second question probably was --

Q. If you can answer either one or a combination or you can ask your own question and then answer it. But you understand my interest is in why is it that you believe some materials to be laboratory carcinogens but you are not persuaded that they are human carcinogens?

A. The demonstration that a substance is a laboratory animal carcinogen does not necessarily imply that it is a human carcinogen, so.

Q. I gather that, but what additional information would you require to be persuaded that

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

something is a human carcinogen?

A. Probably -- the answer is obviously extensive. It involved, you know, a lot of different aspects, but one of them, you know, would be compelling understanding of biological mechanisms of carcinogenic activity and the other extensive support from epidemiological associations.

Q. Okay. Do you believe that cigarette smoking causes lung cancer?

A. I think there is the evidence of -- would support that conclusion, yes.

Q. What is it about cigarette smoking which causes lung cancer?

A. I do not know the answer to that. If I did, I think I'd be a lot better known than I am.

Q. You think it is unknown in science what it is about cigarette smoking which causes cancer?

A. I do.

Q. Really? Do you know it's something about the pyrolysis?

A. I think it's related to the combustion, yes.

Q. Does the cigarette tobacco contain nitrosamines?

A. Restate the question for me, please.

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lqgl0001

Q. Does cigarette tobacco contain nitrosamines?

A. I believe so.

Q. Have those nitrosamines been linked to cancer?

MR. WROBLESKI: Object to the form.

A. Could you repeat the question?

Q. (BY MR. SPOHRER) Yes. Have those nitrosamines been linked to cancer?

MR. WROBLESKI: Same objection.

A. Nitrosamines I believe to be carcinogenic in laboratory animals.

Q. (BY MR. SPOHRER) Do you believe that nitrosamines are carcinogenic in humans?

A. I don't think that's been demonstrated.

Q. Okay. Does smokeless tobacco contain nitrosamines?

A. It does.

Q. Have those nitrosamines been linked to cancer in laboratory animals?

MR. WROBLESKI: Object to the form.

A. Could you restate the question?

Q. (BY MR. SPOHRER) Have those nitrosamines been linked to cancer in laboratory animals?

MR. WROBLESKI: Similar objection.

http://legacy.library.ucsf.edu/tid/vpd07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

A. You mean that nitrosamines present in smokeless tobacco?

Q. (BY MR. SPOHRER) Yes, sir.

A. There is experimental evidence that some of the nitrosamines that are present in smokeless tobacco could elicit a carcinogenic response in laboratory animals.

Q. Do you believe that research?

A. I think that there is some solid data out that would support that it can elicit under certain conditions a carcinogenic response in a laboratory animal.

Q. Okay. And whose work is that?

A. It varied. There is multiple investigators that have conducted some studies.

Q. Any that stand out in your mind?

A. The many of the researchers that originated from the American Health Foundation have conducted those studies.

Q. Dr. Hoffman and Hecht and colleagues?

A. Among them, yes.

Q. Are you aware of what has been referred to as tobacco-specific nitrosamines?

A. I am familiar with that concept, yes.

Q. By that I'm referring to NNN, NNK and NNA.

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

A. Yes, I am.

Q. Are those the nitrosamines that you are making reference to as having been demonstrated as eliciting a carcinogenic response in laboratory animals?

A. Let me sort of qualify the statement that you made.

I think that there is evidence in the scientific literature that some of the tobacco-specific nitrosamines can elicit a carcinogenic response in laboratory animals and as such have been considered to be laboratory animal carcinogens.

Q. Okay. How would a scientist approach an analysis of whether such laboratory carcinogens are human carcinogens? How would you define that research project? How would you go about that?

A. I probably couldn't answer that question because the research I like to conduct does not involve wanting to make an extension from a laboratory observation into human carcinogenesis. Therefore, I really cannot comment.

Q. Okay. Is that question that I just posed something which is knowable in the science, that is, do you believe there are scientists out there who

http://legacy.library.ucsf.edu/tid/vbo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

could devise such a research project to ascertain whether NNN, NNK and NNA are human carcinogens?

A. I don't think so, personally.

Q. Why is that, sir?

A. Well, sort of from a logistical viewpoint you would think that if the experiment was do-able, it would have been done given all of the research that's being conducted. And yet every attempt that has been made, I mean hasn't, you know, really progressed to any significant extent. So I guess the present evidence would argue that, yeah, that it would not be possible to establish.

Q. Obviously, we can't experiment on human beings?

A. Not anymore.

Q. God, when could we?

A. There were times when humans were given -- used experimentally.

Q. Given that state of the science, do you believe it is prudent for us to assume that agents which have been demonstrated as causing cancer in laboratory animals should be avoided by human beings?

MR. WROBLESKI: Object to the form.

A. Could you restate the question?

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the Industry Documents Library: http://www.industrydocuments.ucsf.edu/docs/lggl0001

Q. (BY MR. SPOHRER) I will ask Elaine to read it back because I don't think can do it as well.

A. It was a long question.

(The pending question was read by the Court Reporter.)

A. I believe that from a regulatory perspective that it is the premise that regulate, you know, regulatory agencies use.

Q. (BY MR. SPOHRER) And is that a reasonable premise?

A. It's the premise that we go by. You know because it's attempting to be, I guess, to preempt, you know, a potential problem.

Now, the challenge in this particular issue is that people don't get exposed to nitrosamines alone. So one has to carefully dissect out those relationships.

Q. Understood. Do you believe that nicotine is an addictive substance?

A. I do not have any basis to comment on the addictive qualities of nicotine.

Q. Have you ever studied or considered the addictive properties of nicotine in any context?

A. I have studied the biological effects of nicotine but not within the context of its addictive

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

potential.

Q. Is addiction an illness in your view?

A. That's -- it's beyond what I know so I don't want to comment on it.

Q. Tell me what you meant in your last response when you said that you have considered something about the properties of nicotine?

A. In the past I have examined the ability of nicotine to influence cholinergic transmission but this is something that I did 30 years ago.

Q. Have you -- you haven't done any of this recently then?

A. No, not recently.

Q. How old are you?

A. 46.

Q. You were considering this when you were 16 years old?

A. Actually, when I entered college, yeah. I mean maybe not 16 but certainly 18. I started college when I was 15.

Q. There has been some consideration recently as to whether nicotine itself accelerates the growth of neoplasms. Are you aware of that?

A. I have read some of that literature, yes.

Q. Do you have a view on that?

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lqgl0001

02:21 A. I don't believe the data.

Q. You have in front of you, Dr. Ramos, a three-ring binder, a notebook which contains a number of scientific articles.

02:21 A. Yes.

Q. Where did that come from?

A. This notebook includes articles that were provided to me by Mr. Wrobleski.

Q. And there is a typewritten index in the

02:21 front of that notebook which we have had duplicated here dated November 30, 2000. Is that correct, a bibliography?

A. November 30?

Q. No, that's August. Different one.

02:21 A. August.

Q. Okay. There is a loose index which is the one I had copied dated November 30, 2000, then apparently there was an earlier one dated August of 2000. Okay. In any event, I think they were

02:22 similar. Let me just ask you --

A. They probably should be the same.

Q. Was this index given to you, this bibliography with the notebook and are these the articles that were prepared and given to you by

02:22 counsel?

http://legacy.library.ucsf.edu/tid/vpd07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lqgl0001

A. These are the only articles that, well, this and the report are -- is that my report?

Q. Yes, it is.

A. Are the articles that were given to me by Mr. Wrobleski, yes, and Mr. Kuhlman.

Q. Okay. Have you done any research independent of that, gotten any articles copied on your own?

A. Yes, extensive.

Q. Are those in the pile there as well?

A. Some of them, yeah, are included in here.

Q. Has anybody removed anything from your file?

A. No. Not that I'm aware of, I should say, except maybe what you --

Q. I'm not removing anything. I had it copied, I'm giving it right back to you.

A. May I? Can I take these things back?

Q. Yes, sir, those are yours. I'm going to mark as Exhibit 1 to this deposition the bibliography which we just discussed. And I also have -- this is yours, Doctor?

A. Okay.

Q. -- have here as Exhibit 2 a handwritten note on a little three-inch by three-inch piece of

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lqgl0001

paper. Is that your handwriting?

A. That's correct.

Q. I'm going to mark that as Exhibit 2. Would you read that for us, please?

(Ramos Exhibit Nos. 1 & 2 marked.)

A. Jacksonville, young man, 20 to 25, smokeless, five years, 3.5 years ago, no recurrence, took deposition end of October, complex mixture nitrosamines.

Q. (BY MR. SPOHRER) When did you make that note?

A. I made this note when Mr. Wrobleski first contacted me.

Q. Okay. These are notes you were making while he was speaking to you on the telephone?

A. As he was describing this case, yes.

Q. Okay. What is meant by complex mixture nitrosamines?

A. They are two separate terms actually.

Q. Thank you. Tell me what is meant by the first complex mixture?

A. Complex mixture makes reference to any instance in which you have got multiple chemicals present.

Q. Is this something he was telling you?

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

02:24 A. No, that's something that I probably, you know, wrote.

Q. Okay. Complex mixture meaning nitrosamines, alcohol, other things?

02:25 A. No, sir.

Q. What did you mean by that?

A. When I think of complex mixtures, I think of products that have multiple chemicals present in them. So that's what that term refers to.

02:25 Q. But in this case what is this specific reference to complex mixture?

A. Smokeless tobacco is a complex mixture.

Q. Okay. Then the reference to nitrosamines, what does that mean?

02:25 A. Well, the interaction between, well, it really doesn't mean anything other than the fact that nitrosamines are agents present.

Q. What did Mr. Wrobleski ask of you in that first conversation?

02:25 A. After he described, you know, the case, asked me if I was interested in helping out.

Q. What did you understand your role would be?

A. That if the case progressed, I would be

02:26 asked to give a deposition.

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. industrydocuments.ucsf.edu/docs/lggl0001

02:26 Q. Okay. But in terms of lending your expertise to the case, what did you understand your role would be?

A. To provide expert opinion on the effects of smokeless tobacco in laboratory animals.

02:26 Q. Okay. I did not see in going through your materials any other notes on this case other than a few marginal notes on some articles. Is that correct?

02:26 A. That's correct.

Q. Okay. What opinions have you arrived at with respect to the issues in this case?

A. If you could narrow that question down a little bit.

02:26 Q. Yes, sir. Well, let me just say that you have been identified for us as someone who expects to testify at the trial of this case and I have a disclosure of your areas of expertise. Can you tell us what opinions you have arrived at with respect to

02:27 any of the issues in this case?

A. Any of the issues?

Q. Yes.

A. It would help me out tremendously if you narrow it down for me.

02:27 Q. Well, let me say that I will just read

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

from this document which says "Substance of Facts and Opinions. Dr. Ramos is expected to testify that the studies in which animals were exposed orally to smokeless tobacco do not establish that smokeless tobacco is a laboratory or human carcinogen." Is that an opinion you hold?

A. Yes.

Q. The next sentence reads: "In addition, Dr. Ramos is also expected to testify that those studies do not establish that constituents of smokeless tobacco as found in the product are either laboratory or human carcinogens." Is that also your opinion?

A. It is.

Q. Do you believe that smokeless tobacco contains TSNAs?

A. I believe that it's been demonstrated that TSNAs are present in smokeless tobacco but that doesn't make them carcinogens within the context of the product.

Q. Do you believe that TSNAs are established as carcinogenic in laboratory animals?

A. I believe that TSNAs under a defined set of conditions could elicit a carcinogenic response in laboratory animals, but it's important to qualify

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

02:28 that statement because you could carry out an experiment in which nitrosamines are administered to laboratory animals and you do not get a carcinogenic response, so it is a qualified effect.

02:29 Q. Have there been any laboratory studies that you are aware of which persuade you that TSNAs are carcinogenic in laboratory animals?

A. There have been studies that suggest that nitrosamines are laboratory animal carcinogens, yes.

02:29 Q. Do you find those studies persuasive?

A. With the caveats that I made reference to, yes.

Q. Are those -- tell me which studies those are.

02:29 A. Like I said before, some of the studies that originated from the American Health Foundation.

Q. Okay. Now tell me what the caveats are that you apply to those findings.

A. Some of the caveats, you know, obviously

02:30 not all of them. I guess in -- we could probably talk for months if we went into all the caveats.

Q. I couldn't, but --

A. Some of the most critical caveats with regards to carcinogenicity of nitrosamines relate to

02:30 obviously the dose of the nitrosamine that is used,

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

02:30 relates to the metabolic activation potential of the organism or the system that is being used. And perhaps most relevant to our discussion this afternoon of whether nitrosamines are given alone or 02:31 whether nitrosamines are given in combination with other chemicals, which sort of goes back to the comment I made before about complex mixtures as tobacco smoke and smokeless tobacco are.

Q. You have considered the studies that deal 02:31 with hamsters and rats and placing smokeless tobacco in their pouches?

A. Correct.

Q. You are familiar at least with the consideration of the pH of the mixture and how that 02:31 affects the absorbable nicotine or not?

A. I am familiar with that and that's actually a concept that in this field you learn early on. But it's important to remember that blanket statements about solubility and 02:31 absorbability of a substance cannot be made.

Q. Is there a relationship between the pH of the smokeless tobacco and the amount of absorbable free nicotine?

MR. WROBLESKI: Object to the form.

02:32 A. Tell me the question again.

http://legacy.library.ucsf.edu/tid/vpu07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

02:32 Q. (BY MR. SPOHRER) Is there a relationship between the pH of the smokeless tobacco and the amount of absorbable free nicotine?

MR. WROBLESKI: Same objection.

02:32 A. Is there a relationship between absorbability and pH. In broad chemical terms, the absorption of a substance can be influenced by pH, but it's important to recognize that those measurements have to be carried out under the right 02:32 context. So the context is really what dictates what the outcome is as opposed to the blanket statement that, you know, that pH is going to influence absorbability of the substance.

Q. (BY MR. SPOHRER) Okay. And what is the 02:33 context?

A. For what?

Q. For under what circumstances the amount of absorbable nicotine is affected by the pH?

A. In the context of what?

02:33 Q. I'm using your term, Dr. Ramos. You said one has to carefully consider the context of it. So I'm asking in what context do you want to consider it?

A. I'm answering your question so I cannot 02:33 put context to the question. You need to give me

http://legacy.library.ucsf.edu/tid/vpu07a00/pdf
Support provided by the Industry Documents Library: http://www.industrydocuments.ucsf.edu/docs/lggl0001

02:33 the context.

Q. Do you hold an opinion as to whether or not an increase in pH of smokeless tobacco affects the amount of free nicotine?

02:34 A. In solution?

Q. Yes.

A. So that if you take, let me clarify, I guess. If you take smokeless tobacco and you dissolve it in "X" volume and you adjust the pH

02:34 that's going to change the amount of free nicotine in the solution?

Q. I'm just going to put it in somebody's mouth. I'm not going to dissolve it. Does the pH of that product have an impact on the amount of

02:34 nicotine that's available?

MR. WROBLESKI: Object to the form.

A. I believe that the measurements have to be carried out in the fluids of an individual, you know, in order for you to be able to make a judgment

02:34 as to how much of it is likely to be present in the un-ionized form.

Q. (BY MR. SPOHRER) But I'm not asking you for absolute values as to what's available. I'm just saying is there a relationship between the pH

02:35 and the amount of absorbable nicotine?

http://legacy.library.ucsf.edu/tid/vpu07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

02:35 A. When you say the pH, you mean the pH of the saliva of the individual that's using the product.

Q. The pH of the smokeless tobacco in his saliva?

A. Well, pH is something that's calculated as a function of solubility.

Q. Right.

A. You know, a solid substance doesn't have pH.

Q. So we're going to dissolve the smokeless tobacco in part --

A. In the saliva.

Q. -- in the saliva of the consumer.

A. Okay.

Q. Is that pH value going to have an impact on the absorbable nicotine?

A. From a biological standpoint, the pH of the saliva will influence how much of it is absorbed.

Q. And as that pH is increased, does that result in an increase of the amount of absorbable nicotine?

A. Increased by what?

Q. As it goes up?

http://legacy.library.ucsf.edu/tid/vpg07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

02:36 A. By what? You know, how does the pH go up? Because the fluid, your saliva is going to influence what the pH of the --

Q. Let's just say the pH went up from 6-1/2 to 7-1/2. As that occurs, what is the effect on the amount of absorbable nicotine?

MR. WROBLESKI: Object to the form.

A. So what is the assumption that we're making?

02:36 Q. (BY MR. SPOHRER) You said by how much does it go up. So I'm just giving you some data points. Let's suppose that the pH goes up from 6-1/2 to 7-1/2, does that result in an increase or a decrease in the absorbable nicotine?

02:36 A. What pH?

Q. Of the smokeless tobacco in saliva.

A. Is the pH of the smokeless tobacco or of the saliva?

Q. Both.

02:37 A. That I guess goes back to the point that I was trying to make. The only pH measurement that can be made is that of the fluid, because what you are really looking for when you think of pH is the concentration of hydronium ion in solution so, so we 02:37 really have to talk, I guess, about the pH of the

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

fluid itself.

Q. Okay. Let's talk about the pH of the fluid.

A. Okay.

Q. And the fluid is the saliva?

A. Okay.

Q. And in the saliva is the smokeless tobacco?

A. Okay.

Q. As that pH moves up from 6-1/2 to 7-1/2, what is the resulting effect on the availability nicotine?

MR. WROBLESKI: Object to the form.

A. When you say available, do you mean bio available because available could mean nicotine in the solution; it could mean nicotine in the tobacco.

Q. (BY MR. SPOHRER) I'm talking about the bio availability of the nicotine.

A. Then if you could restate the question for me, I will take it one piece at a time.

Q. As the pH of the saliva with smokeless tobacco in it is increased from 6.5 to 7.5, does that result in a corresponding increase in the bio available free nicotine?

MR. WROBLESKI: Object to the form.

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

A. I think that part of the problem is that as we have sort of digested this issue through, the question sort of becomes more extended and when you extend it, then one has to stop qualifying each piece of that question.

Q. (BY MR. SPOHRER) That's what we have been doing --

A. I know.

Q. -- in response to your asking me to, I have tried to answer your questions and qualify it; and I think we are now at a point where it's answerable and I would like to know your answer, if you have one, sir.

A. I kind of disagree that it's answerable because we have dissected out, but then when the question sort of formulated together, it gets sort of wrapped up again.

Q. Let me just try it one last time. Perhaps we'll have to wait until the trial to get an answer to this, but my question simply is this, sir:

In looking at the bio availability of the free nicotine from moist smokeless tobacco, if the pH of the solution of the consumer's saliva increases, does that result in some increase in the free nicotine?

http://legacy.library.ucsf.edu/tid/vpg07a00/pdf
Support provided by the Industry Documents Library: http://www.industrydocuments.ucsf.edu/docs/lggl0001

MR. WROBLESKI: Object to the form.

A. I don't think that that statement could be made as a blanket statement. There is too many variables to make that prediction.

Q. (BY MR. SPOHRER) Okay. Do you believe that there are any adverse health effects from the use of smokeless tobacco?

A. Personally, I -- I don't know really.

Q. Well, do you have the bottom -- on the bottom there you have the --

A. The report?

Q. Yeah. You have with you, Doctor, the "Health Consequences of Using Smokeless Tobacco," a report to the Advisory Committee to the Surgeon General. Was this given to you by counsel?

A. It was.

Q. Did you highlight the portions here that are highlighted?

A. I did.

Q. In general, do you find this report to be credible?

A. There are sections of it that I agree with and there are sections of it that I disagree with.

Q. Okay. How did you select what to highlight?

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

A. Basically to follow the, you know, the context of the presentation or the comments that were being provided, follow the logic of the document and items that, you know, that -- from a toxicological standpoint were of interest to me.

Q. Let me just read some passages to you and get your comments on them. From the preface:

"After a careful examination of the relevant epidemiologic, experimental and clinical data, the committee concludes that the oral use of smokeless tobacco represents a significant health risk."

Do you agree with that?

A. I believe that the available evidence is very conflictive and erratic and, therefore, inconclusive from my perspective.

Q. Okay. Do you know any of the people on the committee who contributed to this report?

A. Yes, there is some names that I recognize.

Q. Do you know them to be credible scientists?

A. Yes.

Q. Do you believe that the committee that made this report to the Surgeon General had any motivation other than to attempt to understand the

http://legacy.library.ucsf.edu/tid/vpj07a00/pdf
Support provided by the Industry Documents Library: http://www.industrydocuments.ucsf.edu/docs/lggl0001

02:42 scientific and medical literature and make an honest report on that literature?

A. Please restate the question.

Q. Sure. Do you believe that the members of the committee had any agenda other than to attempt to find the scientific truth and report on it?

MR. WROBLESKI: Object to the form.

A. I have no basis to comment on what the agenda or motives of the people in the committee were. I know some of them and I know them to be good scientists.

Q. (BY MR. SPOHRER) Okay, sir, continuing with the preface, paragraph No. 4 states:

"Experimental investigations reveal potent carcinogens in smokeless tobacco. These include nitrosamines, polycyclic aromatic hydrocarbons and radiation emitting polonium."

Do you agree or disagree with that statement?

A. Tell me again the statement. I know that I highlighted it.

Q. That's right. Read it.

A. I think this statement as written could be improved.

Q. Okay. Tell me how you would rewrite it.

http://legacy.library.ucsf.edu/tid/vpg07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

02:43 A. I would, well, I wasn't on the committee, so.

Q. I'm asking you how you would improve it, though.

02:44 A. I definitely would qualify the statement more than it was qualified. You know, it says experimental investigations, well, you know what type of experimental investigation, for instance. I think that ought to have been qualified.

02:44 My presumption, based on what I know, is that the reference was being made to laboratory animal experiments.

I would not have included the word "potent" in this statement. I think it's out of

02:44 context. And the rest, you know, is sort of chemical analysis. Those substances are present in smokeless tobacco.

Q. Okay. So you would qualify the statement by saying -- by removing the word "potent" and by

02:45 saying "experimental investigations in laboratory animals"?

A. Yes. But I must preface that answer by telling you, you know, I wasn't on the committee so that question wasn't asked.

02:45 Q. But that's if you were asked to edit that

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

02:45 sentence or those two sentences, that's how you would edit it?

MR. WROBLESKI: I think the witness would like to see the statement again.

02:45 A. It definitely, you know, the concept of laboratory animal carcinogens should be emphasized in that statement because none of the substances that were listed are anything but laboratory animal.

Q. (BY MR. SPOHRER) Does that include 02:46 radiation emitting polonium?

A. As I mentioned to you, I don't know about, you know, the carcinogenicity of polonium 210 per se other than, you know, the effects of alpha emitting radiation.

02:46 Q. So with respect to the polonium 210, you do not know whether it is considered to be a human carcinogen or not?

A. No, sir. I don't.

Q. If the Atomic Energy Commission classified 02:46 it as a human carcinogen, would you accept that?

A. No, not necessarily. You know, I would have to look at the evidence.

Q. Are you familiar with the IARC, the International Agency for Research on Cancer?

02:46 A. I am.

http://legacy.library.ucsf.edu/tid/vpu07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

Q. Do you know what they have classified TSNAs as?

MR. WROBLESKI: Object to the form.

A. Could you restate the question?

Q. (BY MR. SPOHRER) Sure. Has the IARC classified the TSNAs?

MR. WROBLESKI: Object to the form.

A. Classified as what?

Q. (BY MR. SPOHRER) Has the IARC given a classification to tobacco-specific nitrosamines?

MR. WROBLESKI: Object to the form.

Q. (BY MR. SPOHRER) Are they considered carcinogens by IARC?

A. So the question now is --

Q. These aren't trick questions, Doctor.

A. The question now is whether -- could you restate the question?

Q. Sure. It's not a trick question. It's simply whether, if you know, what the IARC has classified TSNAs as with respect to carcinogenicity?

A. No.

Q. Is that of importance to you in arriving at any opinions here with respect to whether smokeless tobacco is a cancer causing agent?

http://legacy.library.ucsf.edu/tid/vpg07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

A. What is important?

Q. What the IARC has concluded?

A. It's a comment or is a conclusion that obviously has to be considered in formulating an opinion.

Q. Okay. Are you familiar with NTP?

A. I'm familiar with NTP, yes.

Q. Do you know what they have done with respect to tobacco-specific nitrosamines?

MR. WROBLESKI: Object to the form.

Q. (BY MR. SPOHRER) Do you know the classification given by NTP to the tobacco-specific nitrosamines?

A. They agreed with the Surgeon General report.

Q. And do they believe that, well, are they on the "B" list or on the "A" list?

A. I don't know.

Q. Do you have any reason to believe that the National Toxicology Program has any bias or agenda other than to try to find out the scientific truth and to alert the public to potential health hazards?

A. I have no reason to question their agenda.

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

Q. Have you yourself, sir, done any laboratory animal research with respect to whether smokeless tobacco causes cancer?

A. No.

Q. So your work on this issue has been limited to reviewing the research done by others?

A. Correct. Much like I do, you know, in many others aspects of my professional career.

Q. All right. Can you give me just a summary of your conclusions from your review of the animal studies?

MR. WROBLESKI: Object to the form.

A. No. Could you restate the question for me, please?

Q. (BY MR. SPOHRER) There seems to be a pattern here. I ask the question, he objects to the form, you smile and look at me and ask me to repeat the question.

A. Let me tell you what the problem is. I want to make sure I understand your question. As I'm processing the question, I lose my focus when that happens so there is no connection between it.

MR. SPOHRER: Elaine, could you please read the question back because now I have forgotten the question.

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

(The pending question was read by the Court Reporter.)

A. A summary of my conclusions from the animal studies?

Q. (BY MR. SPOHRER) Yes, sir.

A. I believe that the animal studies examining the carcinogenicity of smokeless tobacco do not establish that smokeless tobacco is laboratory animal carcinogen. The data is essentially negative.

Q. Okay. Do you believe that the studies are valid studies? And by that I mean that they were well planned and well executed. Does that make sense to you?

A. It does. No. I actually think many of these experiments were very poorly done.

Q. Okay. Is there a certain inherent difficulty -- is there a certain difficulty inherent in designing an animal study to determine the carcinogenicity of oral tobacco?

A. Yes. There is inherent problems, you know, that have to be carefully accounted for in designing an optimal experiment.

Q. Okay. There are some studies which have shown a negative association. By that I mean

http://legacy.library.ucsf.edu/tid/vpj07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

02:52 studies which have not shown any correlation between smokeless tobacco and carcinogenicity in animal studies. You are aware of those?

A. Yes, I am.

02:53 Q. Do those studies also suffer from the same deficits that you mentioned a moment ago and that is difficulty in planning and executing these studies?

A. Some experiments do, yeah.

Q. So the validity of this whole area of 02:53 study of animal studies and smokeless tobacco use suffers from some deficiencies in your view?

A. In my view, yes.

Q. How would you go about designing an animal study to determine the carcinogenicity of smokeless 02:53 tobacco?

A. Now, this is another one of those questions that we could sit here, you know, and talk for another two days about, you know, the proper design of an experiment --

02:53 Q. Sure.

A. -- but --

Q. First of all before you answer that, let me say, is this the type of question that you consider in your profession?

02:54 A. Yes, this is the type of question that I

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

consider.

Q. Is this the type of study that you could have devised, plan and have executed?

A. Yes.

Q. Has Mr. Wrobleski or anyone on behalf of U.S. Smokeless Tobacco ever come to you and asked you to do such a study?

A. No.

Q. Now, tell me in -- I don't want to spend a month talking about it, but if you could give it to me in sort of a "Readers Digest" version, I would like your thoughts on that, please.

A. A well-designed experiment to assess, you know, carcinogenicity of the product will require an adequate animal model. It will require the inclusion of appropriate controls. And when I mean controls, I mean controls both by way of mode of administration as well as vehicle.

It will require the inclusion of an appropriate number of animals in this study, you know, so that some statistical power can be achieved.

And it will require a clear understanding of the chemical nature of the product that's been examined.

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Digitized by the Internet Archive in 2014 http://www.industrydocuments.ucsf.edu/docs/lggl0001

Q. Okay.

A. And that's -- among many other variables, some of the more critical ones.

Q. What do you believe would be an adequate animal model?

A. For what?

Q. For, to design, to help us in designing a valid study?

A. To examine --

Q. To examine the carcinogenicity or health effects in general of moist smokeless tobacco?

A. Moist smokeless tobacco.

Q. Yes, sir.

A. I guess the short answer is that the right animal model probably is not yet being developed.

Q. I'm sorry, what animal model?

A. The right animal model has not yet been developed so, you know, but I would submit to you that it has to be a model in which the product itself is used. You know, I don't think that studies that examine isolated constituents to reach a conclusion are appropriate. That's inappropriate.

Q. Okay. Pardon me for interrupting. I don't mean to be rude, but my question, I thought,

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

was asking about what type of animal model in your view would be appropriate and by that I was meaning primates versus, you know, other types of animals. Have you given --

A. The reason I sort of got off on that tangent is because in the case of smokeless tobacco, the choice of that animal really would have to be an animal that would be exposed to the product in the way that humans are exposed to if the intent is to assess human risk. And in that context, historical database would argue that there are --

Q. It's hard to get animals to hold this stuff in their mouth?

A. Exactly.

Q. Is there anything about the rat or hamster that has been studied that you believe invalidates those studies?

A. To examine the health effects of smokeless tobacco?

Q. Yes, yes.

A. Certainly, some of the rat experiments are very, very poor experiments.

Q. By that you mean the selection of the animal is poor?

A. That the model itself, you know, not

http://legacy.library.ucsf.edu/tid/vpu07a00/pdf
Support provided by the Industry Documents Library: http://www.industrydocuments.ucsf.edu/docs/lggl0001

02:58 necessarily the rat itself because rats are used all the time in toxicology risk assessment. So rodents in general are useful animal models. But in the case of smokeless tobacco that, you know, there is
02:59 other constraints that go beyond just the selection of a rat.

Q. Are you aware of whether or not anybody has any ongoing research on this subject, the health effects of smokeless tobacco which you believe --
02:59 animal studies which you believe would be more valid than the ones that have been done previously?

A. Not that I'm aware of. No.

Q. Okay. Let's take a five-minute break.

A. Okay.

02:59 (Pause from 3:01 to 3:13 p.m.)

Q. (BY MR. SPOHRER) To summarize what I have drawn from what we have been talking about, you believe that the animal studies relating to smokeless tobacco you believe are inconclusive. Is
03:11 that a fair statement?

A. I believe that the studies, the laboratory animal studies, do not establish the carcinogenicity of this product.

Q. Do they establish the safety of the
03:12 product?

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

03:12 A. I think you almost have to -- know, lack of evidence is no evidence at all. So what -- from a scientific perspective the conclusion to be drawn is that they do not establish the carcinogenicity of the product as a whole.

03:12 Q. Okay. But given the conclusions by the advisory committee to the Surgeon General, given the IARC and NTP classifications, given the work of the American Health Foundation and others, do you

03:13 believe it is prudent for people to avoid smokeless tobacco products, if possible to do so?

MR. WROBLESKI: Objection to form.

A. Regulatory decision making is a very complex process that, that in some instances extends

03:13 beyond what the scientific evidence is.

You know as a toxicologist, what I'm familiar with is the validity of the conclusions regarding the effects of smokeless tobacco in laboratory animals. And my conclusion from that

03:14 scientific literature is in fact -- is in fact consistent with what the Surgeon General report concluded. You know that -- that the studies do not establish carcinogenicity for the product. So, but like I said before, you know, regulatory decision

03:14 making, you know, extends beyond that.

http://legacy.library.ucsf.edu/tid/vpu07a00/pdf
http://www.industrydocuments.ucsf.edu/docs/lggl0001

03:14 Q. You are referring to the Surgeon General's report of what year?

A. 1986.

Q. Okay. Have you been given any additional reports by the Surgeon General on smokeless tobacco?

A. No.

Q. And in response to my earlier question, you said that regulatory decision making is a complex process. I'm not asking you to establish a regulation for all people. I'm asking you whether in your view it is prudent for people in general to avoid smokeless tobacco products and all tobacco products if they are able to do so?

MR. WROBLESKI: Object to the form; asked and answered.

A. I think, you know, the choice to use some of the smokeless tobaccos is a personal choice that people make. You know, it's guided by many different aspects. From a scientific perspective, I don't think that the evidence would support the conclusion that smokeless tobacco is carcinogenic.

Q. Do you hold an opinion within reasonable scientific probability that smokeless tobacco is without risk, is safe?

A. I guess I go back to the statement I made

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

03:15 before: Lack of evidence is no evidence at all. You know, so you almost have to always go to, has it been shown? No. Does that mean that it cannot -- I don't know.

03:16 Q. Okay. Your opinion, I gather, is related to or is limited by your area of expertise which is animal studies. Is that true?

A. It's guided heavily by my expertise, you know.

03:16 Q. Have you considered the epidemiological evidence of the risks of smokeless tobacco?

A. Only to the extent that, you know, that that's summarized in the Surgeon General report. And I look at, you know, the epidemiological

03:16 literature that's in that context, you know, to sort of see how the thought process, you know, was being developed to reach a conclusion.

Obviously, I have reviewed epidemiological literature in the past and from the summary

03:17 statements that were made in the report -- obviously, I have not looked at the primary literature. But from the summary statements that were made, I'm actually very surprised, you know, at the conclusion that was reached on the basis of the

03:17 epidemiology. I found the summary statements that

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

were made conflictive in many instances and in some other instances confounded by inconsistencies in the report.

Now having reviewed other epidemiological literature in the past that was surprising to me, but that's just the nature of the report.

Q. Have you reviewed any clinical data or clinical information in your opinion?

A. No, I have not.

Q. Would that be a valid area of inquiry for consideration?

MR. WROBLESKI: Object to the form.

A. For me?

Q. (BY MR. SPOHRER) For anyone attempting to reach a conclusion with respect to the safety of this product?

A. I would -- my way of thinking in this particular issue is that in order for a conclusion to be reached regarding in this case, you know, carcinogenicity of the smokeless tobacco, one has to take into account, you know, all of the evidence that you have got. Certainly including principles of biological possibility, you know, the consistency of epidemiology and the clinical experience of people, you know, that deal with patients, so.

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

Q. So my question was: Have you considered any clinical data?

A. And I said no.

Q. Okay. But you say it would be important to consider but that is not something you have looked at?

A. It would be an aspect that can be -- that needs to be factored in, yes.

Q. And then with respect to biological plausibility, what is your view?

A. I believe that the experimental evidence that I have reviewed suggests that as, you know, the predicate as a whole, there isn't any biological basis for carcinogenicity, because if there was, you would see it in the laboratory experiments that have been conducted and you don't. So the weight of the evidence is negative for any biological carcinogenic response of the product as a whole.

(Ramos Exhibit No. 3 marked.)

Q. (BY MR. SPOHRER) Dr. Ramos, I have attached as Exhibit 3 to your deposition this typewritten list of your charges. Is that correct?

A. Yes, that's an unbilled summary of my activity to date.

Q. Un what?

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

A. I've never billed for that.

Q. I'm sorry. Okay. Does this reflect all the time that you have spent on this case?

A. Yes.

Q. You are a real bargain for U.S.T., do you know that?

MR. WROBLESKI: Object to the commentary.

Q. (BY MR. SPOHRER) Let me ask, your hourly charge, I gather from this, is $300 an hour?

A. That's correct.

Q. Have you had any trips to New York to visit with counsel on this case?

A. No.

Q. Have you given testimony in other cases other than the three cases in which you have been contacted by Mr. Wrobleski?

A. No, never.

Q. Have you ever testified as an expert witness in a courtroom?

A. No, never.

Q. Have you ever given a deposition before this one?

A. No, never.

Q. Within your field, Dr. Ramos, of

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

03:21 veterinary physiology and pharmacology, you also have an interest in toxicology. Is that correct?

A. I'm actually a toxicologist by training.

Q. Okay.

03:21 A. They just happen to reside in a veterinary and a medical physiology department.

Q. Within those disciplines, do you have a specific area of interest?

A. I do.

03:22 Q. And what is that area or what are those areas?

A. Now let me ask you a question before I answer.

Q. Sure.

03:22 A. Do you mean generically within the field of toxicology or do you mean a specific sort of area of activity?

Q. Well, let's do both. Is there a generic area of interest and then is there a specific one?

03:22 A. My primary interests within the field of toxicology are on molecular biology.

Q. Is there a specific field within that subset that you have an interest in?

A. Yeah. I -- the bulk of my work focuses on

03:22 the regulation of genes and the connection between

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

genetic effects and either animal or human disease.

Q. Do you have an opinion as to what acts upon normal tissue of the tongue to cause it to mutate into a neoplasm?

MR. WROBLESKI: Object to the form.

A. Could you sort of put it into context?

Q. (BY MR. SPOHRER) Yes. Within the field of molecular biology, you have a special interest in the regulation of genes. I'm certain that I'm over-simplifying this, but I understand that in the field of carcinogenesis, it's considered that something acts upon a normal gene to cause it to begin mutating and to develop into a neoplasm. Did I say that correctly?

A. Yes, you did, yes.

Q. Do you hold a view as to what causes or what the causes may be of such carcinogenesis in a tongue cancer such as a squamous cell cancer of the tongue like Mr. McMullin had?

A. I can only answer that question sort of generically because I, you know, I do not work on tongue cancer per se.

Q. Of course.

A. As you know, cancer is many diseases called one. I mean one cancer is not the same as

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

03:24 another cancer.

So with that caveat sort of a qualifier, many things can alter DNA structure which is, you know, what one would think of when you think of mutations. Both endogenous, you know, factors as well as exogenous factors can give rise to altered DNA structure.

Q. Do you hold an opinion as to what the cause of Mr. McMullin's cancer is?

03:25 A. I don't.

Q. You haven't looked at the specific medical issues in this case?

A. Exactly.

Q. Have you looked at or studied P-53 mutations?

A. I have.

Q. In what context?

A. In the context of renal cancer. Both renal cancers of epithelial as well as mesenchymal origin. And I have looked at P-53 mutations in the context of smooth muscle tumors.

Q. Okay. Have you been asked to consider whether there was a P-53 issue in this case?

A. I have not.

03:26 Q. Have you been asked to do any additional

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

work between now and the time of trial?

A. Not specifically, no.

Q. Have you asked for any additional information or material that you need to conclude your opinions?

A. I have not, but that doesn't mean that I will not.

Q. Okay. How did Mr. Wrobleski get your name?

A. Initially, you mean?

Q. Yes, sir.

A. I do not know. I can only speculate.

Q. When was the first approach made to you? Was it over the phone, in writing or in person?

A. I was introduced to Mr. Wrobleski by another lawyer that works in the same firm that he does.

Q. Who is that?

A. His name was or is Michael Davidson.

Q. How do you know Mr. Davidson?

A. He -- he was given my name by a colleague, whom I don't know, and he contacted me by phone some years back.

Q. Had you worked for Mr. Davidson on a case before working with Mr. Wrobleski?

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

03:27 A. I interacted with him, yes.
Q. On what type of issue?
A. Oral cancer.
Q. And was that a case against the U.S. Smokeless Tobacco Company?
A. I do not know.
Q. So when you told me you had two prior cases with Mr. Wrobleski, this is now a third case with that firm. Is that true?
03:28 A. I don't remember. You know, my memory is fuzzy in terms of that. I can tell you for sure about the bladder cancer case that I made reference to initially. And I know for certain, you know, my interactions with Michael and I'm drawing a blank on --
Q. Did you give a deposition for Mr. Davidson?
A. No. Like I said before, I have never given a deposition.
03:28 Q. Okay. But in any event, that case involving Mr. Davidson, Mr. Wrobleski's colleague, involved a claim of someone who had developed oral cancer from using smokeless tobacco?
A. It was, yeah, a case of a woman, a very
03:29 old woman that developed oral cancer.

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

03:29 Q. Looking at your note here on chapter 2, principles of toxicology. Can you see that in your materials?

A. Yes.

03:29 Q. What did you write up at the top of that page?

A. I said Cancer Rate and Dual Toxicology, the Basic Science of Poisons, fifth edition (sic).

Q. That's the title of the text book?

03:29 A. Correct, where this was taken.

Q. Why did you copy this?

A. I copied this because I wanted to, you know, sort of revisit the whole concept of, you know, acute versus sub-acute versus subchronic and

03:30 chronic, and that's really the only basis for me to copy it.

Q. Okay. The next article that I have pulled is "The Effects of Smokeless Tobacco on the Buccal Mucosa of HMT Rats."

A. Yeah.

Q. You see that?

A. Yeah.

Q. This is one of the articles that you considered?

03:30 A. This is one of the articles that I read,

http://legacy.library.ucsf.edu/tid/vbo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

yeah.

Q. Okay. Were you give this by Mr. Wrobleski or was this something that you pulled yourself?

A. I would assume this is something that I must have pulled out myself, you know, because it's not in the binders, so.

Q. Okay. The authors conclude, just reading from the summary at the top, "Results indicate that the effects of smokeless tobacco on the rat buccal mucosa are similar to those observed in humans and that the mitotic process can be disturbed by tobacco treatment." This is dated 1989.

A. Okay.

Q. You wrote at the top of this "check on this rat"?

A. Yeah.

Q. What did you mean by that?

A. I was not familiar with the HMT rat. That's a strain. And that's all I meant by checking on the rat.

Q. At the bottom you said "genetic background of the rats, check epithelial --"

A. Red pegs.

Q. What?

A. Red pegs.

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

Q. What does that mean?

A. That's a term that's used in pathology to describe, you know, epithelial morphology.

Q. So did you check on the background of these rats?

A. Not yet.

Q. Is this study invalid in your view?

A. I would need to reread the study to sort of, you know, know the details of it. And I haven't, so.

Q. Well, could we just go through it here briefly while you are -- you have highlighted portions here. You underlined portions of the study.

A. Yeah.

Q. You made marginal notes. Did you conclude that this study was not valid, not reliable?

A. Like I said, I really need to go back and read the article, you know, again. You know, it's been a while since I read it. So I would need to sit down and read, you know, the paper.

Q. Well, I mean I guess I'm just curious about your notes on this page. This is a study which apparently the authors have concluded that smokeless tobacco does have an effect on the cheek

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

of these rats and causes a problem which the authors say is similar to that observed in humans.

And your notes seem to be indicating that you want to check on the rat and check on the epithelial red peg and try to distinguish this rat or this analysis to discredit it or to distinguish it from the other articles. Is that true?

MR. WROBLESKI: Object to the form.

A. Actually, when I made the note, it was more out of scientific, you know, curiosity because I, you know, with all the reading I do on this particular subject, it was a strain of rats that I just had never seen and, you know, it was more an intellectual exercise than anything related to the effects of smokeless tobacco, you know. There is no connection between that note and the contents of the paper.

Q. (BY MR. SPOHRER) Okay. Well, let me ask you if you accept or reject the author's conclusions with regard to the effects of smokeless tobacco on this particular laboratory animal?

MR. WROBLESKI: Object to the form.

A. Like I said, I really need to reread the paper and, you know, reexamine in order to comment and answer your question.

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. industrydocuments.ucsf.edu/docs/lggl0001

03:34 Q. (BY MR. SPOHRER) In how many studies did you find that the authors concluded that the use of smokeless tobacco caused adverse health effects on laboratory animals?

03:34 A. There are some studies, you know, that report on adverse health effects in laboratory animals.

Q. Okay. Do you reject the conclusions of all of those authors?

03:35 A. Like I said, you know, we would have to go paper by paper to sort of, you know, dissect out the information, but you know, there may be morphological changes that, you know, there is evidence for and that, oh, yeah, there is, you know, an alteration in the morphology of the cells. But you know, we would have to go study by study.

Interestingly though, even in this article that's here, you know, these are sort of morphological alterations, none of which relate to, you know, directly to cancer of the oral cavity. So from that perspective, you know, this study doesn't shed any light on carcinogenesis.

Q. Well, I guess I'm here taking your deposition and you have been listed as an expert to

03:36 testify to the effect that the studies do not

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

03:36 establish that smokeless tobacco is a laboratory or human carcinogen.

Let me ask you first what, what would you require to feel that that was established, that 03:36 smokeless tobacco is either a laboratory or a human carcinogen?

MR. WROBLESKI: Object to the form.

A. Many things would be required, but I think the bottom line would be that I would expect to see 03:36 consistency in the results and I would expect to see reproducibility of the results from across different laboratories. And I would expect to see an experiment that is well designed and well executed. You know, and many of those are lacking.

03:37 Q. (BY MR. SPOHRER) Why is it that that hasn't been done, to your knowledge?

A. I do not know, although it's a question that I have myself. You know, I have asked myself that same question. My conclusion from it -- 03:37 actually, not a conclusion. My impression is that the effect's not there and, therefore, hasn't been described.

Q. Well, but we have discussed how you question the validity of all of the studies that 03:38 have been done, the ones that have had positive

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

03:38 results and the negative results. Is that right?

MR. WROBLESKI: Object to the form. Mischaracterizes his testimony.

A. When one, you know, I think the important aspect of this discussion from my perspective is the answer to the hypothesis, right? So you pose a hypothesis and you do experiments to challenge the hypothesis.

The hypothesis is, in many instances, that smokeless tobacco will cause tumors in laboratory animals, whether it be a rat, a hamster, you know, a monkey or a mouse. The experiment is designed. You hope the terminal design is adequate and we fully discuss that in many instances -- in most instances it is not.

And when the answer that you get is that there is no tumors or that the numbers of tumors that were found is statistically insignificant relative to the population that was examined or that the experiment has confounders that invalidate the conclusion, then you are left with a hypothesis for which you have no support. And I think that describes this area of activity.

The studies that have been completed to date are either poor or have not shown

http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

03:39 carcinogenicity of this product.

Q. (BY MR. SPOHRER) Okay. With respect to your conclusions, have you communicated them to the IARC or the NTP?

03:40 A. I have not.

MR. SPOHRER: That's all I have. Thank you, Doctor. Nice meeting you.

A. Okay. Same here.

(Concluded at 3:42 p.m.)

http://legacy.library.ucsf.edu/tid/vpo07a00/pdf
Support provided by the UCSF Industry Documents Library. http://www.industrydocuments.ucsf.edu/docs/lggl0001

CHANGES and SIGNATURE DEPOSITION of
KENNETH RAMOS, Ph.D.

PAGE	LINE	CHANGE	REASON

_____

KENNETH RAMOS, Ph.D.

http://legacy.library.ucsf.edu/tid/vnb07a00/pdf
Support provided by the UCSF Library
https://www.industrydocuments.ucsf.edu/docs/lggl0001

I, KENNETH RAMOS, Ph.D., have read the foregoing deposition and hereby affix my signature that same is true and correct, except as noted above.

_____
KENNETH RAMOS, Ph.D.

THE STATE OF TEXAS)

COUNTY OF HARRIS)

Before me, _____, on this day personally appeared KENNETH RAMOS, Ph.D., known to me or proved to me under oath or through _____ to be the person whose name is subscribed to the foregoing instrument and acknowledged to me that they executed the same for the purposes and consideration therein expressed.

Given under my hand and seal of office this _____ day of _____, 2002.

_____
NOTARY PUBLIC IN AND FOR
THE STATE OF TEXAS

My Commission Expires:_____

http://legacy.library.ucsf.edu/tid/vnb07a00/pdf industrydocuments.ucsf.edu/docs/lggl0001

THE STATE OF TEXAS :

REPORTER'S CERTIFICATE

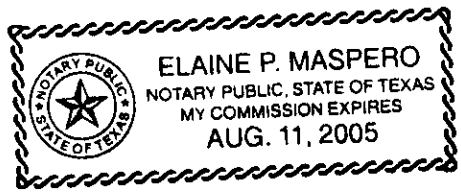
I, Elaine P. Maspero, Certified Shorthand Reporter and Notary Public in and for the State of Texas, hereby certify that this deposition transcript is a true record of the testimony given by the witness, KENNETH RAMOS, Ph.D., after said witness was duly sworn or affirmed by me.

I further certify that I am neither attorney nor counsel for, related to, nor employed by any of the parties to the action in which this testimony was taken. Further, I am not a relative or employee of any attorney of record in this case, nor do I have a financial interest in the action.

Certified to on this 9th day of October, 2002.

Elaine P. Maspero

Elaine P. Maspero, CSR #320
Notary Public in and for
The State of T e x a s
Certification expires 12-31-02
Commission expires 8-11-05



http://legacy.library.ucsf.edu/tid/vpb07a00/pdf
Support provided by the UCSF Industry Documents Library. industrydocuments.ucsf.edu/docs/lggl0001